REMARKS

I. Support for the amendment to claim 1 can be found in the specification, for example, at page 13, 3rd paragraph; pages 29-31; page 33, last paragraph; pages 35-37; and in original claims 6 and 29. Thus, as no issue of new matter is triggered by the amendment, entry thereof is requested respectfully.

Claims 1-3, 27, 31, 36, 40 and 49 read on the elected species of lentivirus.

II. On page 5 of the Office Action, claims 1-3, 5, 6, 27-31 and 36-42 were rejected provisionally under the judicially-created doctrine of obviousness-type double patenting over claims 1-3, 27, 28, 30-32, 38-41, 45 and 51-62 of U.S. Ser. No. 10/080,797.

Applicants respectfully disagree. However to expedite prosecution, Applicants will consider filing a Terminal Disclaimer on indication of otherwise allowable subject matter.

III. On page 6 of the Office Action, claims 1-3, 5, 6, 31, 36 and 41 were rejected provisionally under the judicially-created doctrine of obviousness-type double patenting over claims 1-4, 9, 11 and 16 of U.S. Ser. No. 10/529,428.

Applicants respectfully disagree. Nonetheless, the '428 application was filed after the subject application. Accordingly, on an indication of otherwise allowable subject matter, the instant provisional obviousness-type double patenting rejection should be withdrawn, and the subject application should be allowed to issue as a patent without a terminal disclaimer. (MPEP §804(I)(B)(1), Rev. 5, Aug. 2006, page 800-17, right column.)

IV. On page 7 of the Office Action, claims 1, 5, 6 and 31 were rejected provisionally under the judicially-created doctrine of obviousness-type double patenting over claims 52-56 and 59 of U.S. Ser. No. 10/910,293.

In view of the claim amendments incorporating elements of non-rejected claim 29 into the base claim, withdrawal of the rejection is in order.

V. On page 8 of the Office Action, claims 1-3 and 5 were rejected under 35 U.S.C. 112, second paragraph. The Examiner opined that an essential step was missing, that is, he was unclear how the effecting is being accomplished. (Office Action, page 8.)

In view of the amendment to claim 1, withdrawal of the rejection is in order.

VI. At the bottom of page 8 of the Office Action, claim 33 was rejected under 35 U.S.C. 112, second paragraph. The Examiner stated that the phrase, "at least about," is indefinite.

Applicants respectfully disagree. However, claim 33 has been cancelled thereby rendering the rejection moot.

VII. On page 9 of the Office Action, claims 1-3, 5, 6 and 27 were rejected under 35 U.S.C. 102(b) over Leboulch et al. as evidenced by Chu et al. Then in a second novelty rejection, on page 11 of the Office Action, claims 1, 5 and 6 were rejected as anticipated under 35 U.S.C. 102(a) over Mori et al.

Applicants disagree with both rejections under 35 U.S.C. 102, but solely to advance prosecution, and not in acquiescence to the rejections of the Examiner, the claims were amended to recite, "...subretinal injection of an effective amount of a viral vector comprising an endostatin-encoding nucleic acid." Neither Leboulch et al. nor Mori et al. disclose subretinal injection.

Thus, novelty is not disturbed and the rejections under 35 U.S.C. 102 are to be removed.

VIII. On page 13 of the Office Action, claims 1, 5, 6, 31, 36 and 37 were rejected under 35 U.S.C. 103(a) over Leboulch et al. in view of the '107 patent.

The rejection is traversed for the following reasons.

To establish prima facie obviousness of a claimed invention, an Examiner must show that all the claim limitations are taught or suggested by the prior art. (In re Royka, 490 F.2d 981, 985 (Fed. Cir. 1974).)

Solely to advance prosecution, and not in acquiescence to the rejection of the Examiner, claim 1 was amended to recite, "…wherein the increase is effected by a subretinal injection of an effective amount of a viral vector." The amendment incorporates the subject matter of non-rejected claim 29. Additionally, neither Leboulch et al. nor the '107 patent disclose or suggest subretinal injection.

Hence, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103(a).

IX. On page 16 of the Office Action, claims 21, 28-30 and 37-40 were rejected under 35 U.S.C. 103(a) over Leboulch et al. in view of the '107 patent, and further in view of the '826 patent of Brandt.

The rejection is traversed for the following reasons.

As stated hereinabove, neither Leboulch et al. nor the '107 patent disclose or suggest subretinal injection.

The Examiner stated, "Brandt et al. teach subretinal . . .injection for treatment of ocular diseases." (Office Action, page 18.)

However, a closer review of the reference as a whole reveals that Brandt et al. teach away from the use of subretinal injection in the eye.

Brandt et al. mention subretinal injection twice. At the top of column 4, Brandt et al. stated, "…[s]o far, researchers have only been able to 'label' retinal cells, via subretinal injection, which causes retinal detachment in the area of the injection."

That statement concludes that at the time, the only way to label retinal cells was subretinal injection. However, that singular available means for labeling retinal cells was not without a significant side effect, namely, retinal detachment.

Thus, Brandt et al. teach away from the claimed invention of using a viral vector since at the time of the invention, one skilled in the art would have wanted to **avoid** retinal detachment.

Additionally, the "labeling" of a cell in Brandt et al. was done with a non-secreted protein and is therefore distinct and less complicated than having a cell of the eye properly express a secreted protein from an introduced vector carrying a nucleic acid encoding the same.

The second reference to subretinal rejection in Brandt et al. stated:

> "...[f]or example, subretinal or intravitreal injection of a number of growth factors, cytokines and neurotrophins . . . have been shown to restore specific functions to retinal or retinal pigment epithelial cells and to retard photoreceptor cell death in various animal models of retinal degeneration. Faktorovich et al., Nature 347:83 (1990); LaVail et al., Proc. Nat'l Acad. Sci. USA 89:11249 (1992)." (Middle of column 8.)

The abstracts of both of Faktorovich et al. and LaVail et al. only refer to the injection of protein and not of vector. Therefore, the second reference to subretinal rejection in Brandt et al. solely refers to the injection of protein and not to injection of vectors that express the protein. Injection of protein avoids any potential problems and uncertainty that might be associated with expressing and secreting a protein at the desired area of the eye.

As a whole, Brandt et al. would not suggest subretinally injecting a vector expressing a protein, such as endostatin, that requires secretion from the transduced cell. Instead, as advanced above, Brandt et al. teach away from that approach. Neither Leboulch et al. nor the '107 patent cure those fatal deficiencies and the teaching away of Brandt et al. Hence, based on the cited documents, the claimed subject matter would not have been obvious at the time of invention. Accordingly, for those reasons, a prima facie case of obviousness has not been made.

Additionally, the Examiner must show that there is a reasonable expectation of successfully combining the teachings of the references. (In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991))

Neither Leboulch et al. nor the '107 patent disclose subretinal injection of a viral vector. The Examiner provided Brandt et al., which makes passing mention of subretinal injection as a type of injection known in the art, for allegedly curing that deficiency of the primary references. However, following the guidance provided by the In re Vaeck decision, the three documents can only be properly combined if on considering those documents, an artisan would have had a reasonable expectation of successfully obtaining the claimed invention.

However, as explained above, the three cited documents do not provide a reasonable expectation of success with regard to treating retinal edema by subretinal injection of an effective amount of a viral vector comprising an endostatin-encoding nucleic acid to an individual. Moreover, there were other potential issues related to treating retinal edema by a subretinal injection of an effective amount of a viral vector encoding endostatin. Some of those issues are as follows.

For example, it was not known if subretinal injection of a viral vector encoding endostatin would transduce a sufficient number of ocular cells to express an effective amount of endostatin. For example, in Mori et al., an adenoviral vector expressing endostatin was used to transduce liver cells of a mouse. It was known that adenoviral vectors readily transduce a relatively large number of liver cells and thus express high levels of a transgene. For example, Figures 1A and 1B of Mori et al. demonstrate that endostatin expressed by liver reached levels of 10 μg/ml and higher, in serum.

It was not known at the time of the invention if a subretinal injection of a viral vector, which will typically transduce several orders of magnitude less cells than the i.v. injection of Mori et al., could achieve effective levels of endostatin expression.

Additionally, the results in Mori et al. were achieved with high levels of endostatin in serum. Endostatin expressed via a subretinal injection would not have been expected to achieve a significant level of endostatin in serum, let alone an effective local amount. Moreover, it was not known if the endostatin produced via subretinal injection of a vector could reach the same

effective area of the eye as did the endostatin produced from liver cells as in Mori et al. Even if some endostatin from the subretinally injected endostatin vector reached the effective area, it could not be known if an effective amount would reach that affected area of the eye.

Clearly, subretinal injection of a viral vector will transduce completely different cell types that those transduced by i.v. injection for infecting liver cells of Mori et al. It was not known at the time of the invention if cells of the eye transduced by subretinal injection would express effective amounts of endostatin or, for that matter, would be able to secrete endostatin. Furthermore, it was not known if: (i) endostatin would diffuse from the endostatin-producing cells to the local area of retinal leakage; (ii) cells would secrete endostatin from the correct "side" of the cells, since many cells of the eye are polarized; or (iii) the endostatin would diffuse in the proper direction only to be flushed away, e.g., directly into the choroid, before effective levels could be reached at the site requiring treatment.

In addition, it was not known if cells of the eye, such as the retinal pigment epithelial cells or photoreceptor cells, could express and secrete endostatin without disrupting any of the highly specialized functions of those cells, and without causing significant pathology. It was not known (i) whether the endostatin produced by ocular cells would be functional and/or stable and (ii) if endostatin would be degraded at a rate that would not allow effective local levels of endostatin for treatment of retinal edema to be achieved.

Finally, as noted above, Brandt et al., teach that subretinal injection causes retinal detachment in the area of injection. (Brandt et al., column 4, lines 7-10.) Prior to the claimed invention, it was not known if such detachment from injecting an endostatin viral vector would still allow for an effective amount of endostatin to be secreted from the cells, e.g., it was not known whether a significant number of the detached cells would die or would be too unhealthy to secrete effective amounts of endostatin.

It is clear that until the present invention, those skilled in the art did not have a reasonable expectation that the claimed invention could be practiced or utilized to treat retinal edema in an individual. Based on any one of the reasons above, there would not have been a reasonable expectation of success with regard to the claimed invention.

Thus, for those additional reasons, it is clear that the claimed invention would not have been obvious and thus, a prima facie case of obviousness has not been made. Instead, the wholly unexpected observation that subretinal injection of a viral vector expressing endostatin can yield effective levels of endostatin in the proper site(s) in the eye to treat retinal edema, speaks to the non-obviousness of the instant invention.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103(a).

X. At the bottom of page 19 of the Office Action, claims 41 and 42 were rejected under 35 U.S.C. 103(a) over Leboulch et al. in view of the '107 patent, and further in view of Clark et al.

Applicants respectfully disagree. However, claims 41 and 42 were cancelled rendering the rejection moot.

XI. At the bottom of page 22 of the Office Action, claims 32-35 were rejected under 35 U.S.C. 103(a) over Leboulch et al. in view of the '107 patent and further in view of Mori et al.

Applicants respectfully disagree. However, claims 32-35 were cancelled rendering the rejection moot.

CONCLUSION

Applicants respectfully request reconsideration, withdrawal of the rejections and early indication of allowance. If any questions remain, the Examiner is requested to contact the undersigned at the local exchange noted hereinbelow.

Respectfully submitted,

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